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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/698,323	10/27/2000	Jeffrey M. Isner	47624-DIV (1417)	6299
21874	7590	05/20/2003		
EDWARDS & ANGELL, LLP P.O. BOX 9169 BOSTON, MA 02209			EXAMINER	NGUYEN, QUANG
			ART UNIT	PAPER NUMBER
			1636	16
			DATE MAILED: 05/20/2003	

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	09/698,323	ISNER ET AL.
	<b>Examiner</b>	<b>Art Unit</b>
	Quang Nguyen, Ph.D.	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 05 March 2003.

2a) This action is FINAL.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 50,52,55-63,65-68,70 and 72-81 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 50,52,55-63,65-68,70 and 72-81 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____	6) <input type="checkbox"/> Other: _____

### **DETAILED ACTION**

Applicants' amendment filed on 3/05/03 in Paper No. 15 has been entered.

Amended claims 50, 52, 55-63, 65-68, 70 and 72-81 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

#### ***Claim Rejections - 35 USC § 102***

New claim 81 is rejected under 35 U.S.C. 102(b) as being anticipated by Pu et al. (Circulation 88:208-215,1993) or Franco (U.S. Patent 4,296,100) or Kawakami et al. (Brain Res. 697:104-111, 1995) or Ferrara et al. (U.S. Patent 6,133,231) for the same reasons set forth in the previous Office Action.

#### ***Response to Arguments***

In the Amendment filed on 3/05/03 in Paper No. 15 (pages 6-7), with respect to the above cited prior arts Applicants basically argue that the amended claims do not feature the use of FGF or HGF. New claim 81 still recites the use of FGF and HGF, and therefore the claim rejected for the same reasons already set forth in the previous Office Action.

#### ***Claim Rejections - 35 USC § 103***

Amended claims 50-52, 55-63, 65-68, 70, 72-79 and 81 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al. (U.S. Patent 5,880,090, IDS from 09/265041) in view of Asahara et al. (Science 275:964-967, 1997, IDS from 09/265041) or Isner et al. (U.S. Patent No. 5,980,887 with the effective filing date of 11/8/1996).

Hammond et al. teach that upon administering an agent selected from the group consisting of stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) into a graft recipient, bone marrow-derived CD34+ endothelial progenitor cells are mobilized into the blood stream (increase in the concentration of the progenitor cells) and to enhance the endothelialization of synthetic vascular grafts (See abstract and example 3 in column 9). Hammond et al. also teach that more than one endothelialization-promoting agent (e.g., fibroblast growth factors, VEGF, angiopoietin) may be administered concomitantly, and the agent may be administered to the intended graft recipient as much as seven days prior to implantation of the graft, or may begin on the same day as graft implantation (see col. 3, lines 57-67; col. 4, lines 32-40). An exemplified used dosage for G-CSF is from about 5ug to 15 ug/kg body weight for a total of 3 to 5 days (col. 4, lines 24-31), which is within the preferred dosage range of vascularization modulating agents of the presently claimed invention (1 ug/kg/day to about 100 ug/kg/day).

Hammond et al. do not teach specifically a method for inducing formation of new blood vessels, or reducing the severity of blood vessel damage or enhancing EPC mobilization in a mammal having chronic or acute ischemia using GM-CSF.

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However, Hammond et al. noted that Asahara et al. have shown CD34+ endothelial cell populations are capable of differentiating into endothelial-like cells and the circulating CD34+ or Flk-1+ cells may participate in the repair of ischemic tissue (column 3, lines 28-37). In animal models of ischemia (mouse and rabbit models of induced unilateral hindlimb ischemia), Asahara et al. already teach that syngeneic or autologous endothelial cell progenitors are incorporated into capillaries and small arteries in the neovascular zones of the induced ischemic limb (See abstract and page 966). Isner et al. also teach the use of EC progenitors to induce reendothelialization of an injured blood vessels or treating an injured blood vessel in a patient resulting from surgery (balloon angioplasty or deployment of an endovascular stent) or from an ischemic tissue (e.g. cerebrovascular ischemia, renal ischemia, pulmonary ischemia). Isner et al. further teach the use of EC progenitor cells can be used in combination with an endothelial cell mitogen such as VEGF, FGFs, HGF, nitric oxide synthase among others (see the entire patent and the claims).

Accordingly, at the time of the instant invention it would have been obvious to an ordinary skilled artisan to modify the method disclosed by Hammond et al. by administering into a mammal having an chronic or acute ischemia instead of a recipient of a synthetic vascular graft an agent selected from the group consisting of SCF, GM-CSF and G-CSF to mobilize an effective level of bone marrow-derived endothelial progenitors to home into sites of active angiogenesis to repair ischemic tissues by forming new blood vessels as taught by Asahara et al. or Isner et al.

One of ordinary skilled in the art would have been motivated to carry out the above modification to avoid the tedious and time-consuming isolation and purification of progenitor endothelial cells. Since the modified method has the same step and same active components (e.g., GM-CSF, G-CSF, SCF) with an effective dosage within the preferred dosage range of vascularization modulating agents used in the presently claimed invention, the modified method would also result in an increase in endothelial progenitor cell frequency and differentiation, as well as an increase in blood vessel length and blood vessel diameter, and an increase in EPC incorporation into foci in the treated mammal.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

### ***Response to Arguments***

Applicants' arguments related to the above rejections in the Amendment filed on filed on 3/05/03 in Paper No. 15 (page 7) have been fully considered.

Applicants argue basically that the amended claims include the language of the previous claim 54, now cancelled, which was not rejected as obviousness in view of the cited art, and therefore the rejection has been rendered moot. Applicants' argument is respectfully found to be unpersuasive for the following reason. The previous claim 54 recites the phrase "a standard EPC culture 2 5 assay" and it was found to be unclear and therefore it was rejected under 112 second paragraph. Because the metes and bounds of the previous claim 54, now cancelled, were not clearly determined and

therefore no prior art was applied. It is further noted that the amended claims now recite "a standard EPC culture assay" not "a standard EPC culture 2 5 assay".

Accordingly, amended claims 50-52, 55-63, 65-68, 70, 72-79 and 81 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al. in view of Asahara et al. or Isner et al. for the same reasons set forth above.

***Following is a new ground of rejection necessitated by Applicants' amendment.***

***New Matter***

New claim 80 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 80 recites "The method of claim 50 further comprising isolating EPCs from the mammal and administering the EPCs to the mammal". There is literal no support in the originally filed specification for Applicants' contemplation specifically for the method of the new claim 80. Line 20 at page 8 to line 1 at page 9 of the present application (see Amendment filed on filed on 3/05/03 in Paper No. 15, page 4) do not support for the steps of the method as claimed in newly added claim 80. Therefore, given the lack of written support for a method of inducing formation of new blood vessels in a mammal having

chronic or acute ischemia with the steps as recited, it would appear that Applicants did not have possession of the claimed invention at the time the application was filed.

***Claim Rejections - 35 USC § 112***

New claim 80 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth immediately above. As enablement requires the specification to teach how to make and use the claimed invention, with the lack of sufficient description and/or guidance provided by the instant specification at the time the application was filed regarding to the method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia having the recited steps, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57-58, 65-67 and 80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 57 and 58 are dependent on the cancelled claim 53. Therefore, it is unclear what exactly Applicants want to claim. Similarly, claims 65-67 are dependent

on the cancelled claim 64. It is also unclear what exactly Applicants want to claim. For the purpose of compact prosecution, Examiner interprets claims 57-58 and 65-67 to be dependent on claim 50. Furthermore, assuming that claims 65-67 to be dependent on claim 50, there is a potential lack of antecedent basis in the claims for the phrase "the ischemic tissue".

In claim 80, the phrase "further comprising isolating EPCs from the mammal and administering the EPCs to the mammal" renders the claim indefinite. This is because a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia has been completed upon administering to the mammal an effective amount of a VEGF or a hematopoietic factor.

#### ***Claim Rejections - 35 USC § 102***

Amended claims 50 and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Takeshita et al. (J. Clin. Invest. 93:662-670, 1994; IDS).

Takeshita et al. teach a method of administering VEGF at doses of 500-1,000 ug as a single intraarterial bolus to the internal iliac artery of rabbits in which the ipsilateral femoral artery was excised to induce severe, unilateral hind limb ischemia (see abstract and the entire article). Since the disclosed method of Takeshita et al. has the same step as the instant claimed method (administering to a mammal having chronic or acute ischemia an effective amount of a VEGF), and that the utilized dosage is within the preferred dosage range of contemplated by Applicants, an increase in endothelial

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progenitor cell frequency and differentiation would be inherent results of the method taught by Takeshita et al.

Therefore, Takeshita et al. anticipate the instant claims.

### ***Conclusions***

#### ***No claims are allowed.***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

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To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.



DAVID GUZO  
PRIMARY EXAMINER